Effects of Micronutrients on Metal Toxicity

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There is growing evidence that micronutrient intake has a significant effect on the toxicity and carcinogenesis caused by various chemicals. This paper examines the effect of micronutrient status on the toxicity of four nonessential metals: cadmium, lead, mercury, and arsenic. Unfortunately, few studies have directly examined the effect of dietary deficiency or supplementation on metal toxicity. More commonly, the effect of dietary alteration must be deduced from the results of mechanistic studies. We have chosen to separate the effect of micronutrients on toxic metals into three classes: interaction between essential micronutrients and toxic metals during uptake, binding, and excretion; influence of micronutrients on the metabolism of toxic metals; and effect of micronutrients on secondary toxic effects of metals. Based on data from mechanistic studies, the ability of micronutrients to modulate the toxicity of metals is indisputable. Micronutrients interact with toxic metals at several points in the body: absorption and excretion of toxic metals; transport of metals in the body; binding to target proteins; metabolism and sequestration of toxic metals; and finally, in secondary mechanisms of toxicity such as oxidative stress. Therefore, people eating a diet deficient in micronutrients will be predisposed to toxicity from nonessential metals. — *Environ Health Perspect* 106(Suppl 1): 203–216 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-1/203-216peraza/abstract.html*

Key words: metal toxicity, micronutrient(s), diet, cadmium, lead, mercury, arsenic

Introduction

Research on the effects of micronutrients on toxicity and carcinogenicity caused by various chemicals has produced growing evidence in the field of micronutrient intake and reduction of toxicity. We have reviewed the literature on this topic; however, few studies have directly examined the effect of dietary deficiency or supplementation on metal toxicity. More commonly, the effect of dietary alteration must be deduced from the results of mechanistic studies.

This paper examines the effects of micronutrients on the toxicity of cadmium, lead, mercury, and arsenic — four nonessential metals. The effects of micronutrients on these metals are separated into three classes. The first class deals with the interaction between essential micronutrients and toxic metals during uptake, binding, and excretion. The second class deals with the influence of micronutrients on the metabolism of these toxic metals. The third class describes the effect of micronutrients on secondary effects of metals.

Micronutrients can affect toxicity of metals by interacting with the metal at its primary site of action. Examples of this type of interaction include the effects of calcium on lead, phosphate on arsenate, and zinc on cadmium. In these cases the toxic metal exerts its effect by interfering with the action of the essential compound. By this argument, increasing the availability of the essential micronutrients should decrease the toxicity of toxic metals. More lead is absorbed by people on a calcium-poor diet than by those on a calcium-rich diet.

Micronutrients can also modify the body's response to toxic metals by altering their metabolism and transport. Methionine can prevent methylmercury central nervous system (CNS) toxicity by blocking transport of the methylmercury–cysteine complex into the brain via the large neutral amino acid transporter. Zinc increases synthesis of metallothionein (MT), a thiol-rich protein that sequesters cadmium and prevents acute hepatotoxicity, leading instead to chronic kidney toxicity as cadmium-MT is excreted from the liver and absorbed by the kidney.

Finally, there are a number of other possible interactions of micronutrients with secondary mechanisms of toxicity of nonessential metals. An example of this is the protective effect of vitamin E on methylmercury toxicity. Vitamin E is an antioxidant and prevents free radical injury caused by methylmercury.

Nutrition and Its Effects on Cadmium Toxicity

Cadmium, a group IIB metal on the periodic table, is a nonessential trace element. It is present as a contaminant in food (leafy vegetables, grains, and cereals), water, and tobacco leaves, as well as being a byproduct of zinc and lead mining and smelting. Because of its widespread nature, cadmium can either be ingested via contaminated foods or inhaled. Even in small amounts (~200 ppm) significant damage occurs to the kidneys and to the gastrointestinal tract in mammals (*1*). Other manifestations of cadmium toxicity include mild anemia and osteoporosis. The most pronounced effects occur in the kidney. Only when significant cadmium damage such as proteinuria and decreased renal function has occurred does significant cadmium excretion occur. Unfortunately, there are few if any symptoms of chronic exposure to small amounts of cadmium. Therefore, by the time symptoms are apparent, hypertension or coronary artery disease may exist in the cadmium-intoxicated patient. Increased cadmium levels are associated with coronary artery disease, hypertension, emphysema, and other chronic pulmonary diseases. This could be the reason cigarette smokers are more prone to acquiring hypertension, coronary artery disease, and emphysema (*2*).

The most dangerous characteristic of cadmium is that it accumulates throughout a lifetime. Cadmium accumulates mostly in the liver and kidney and has a long biological half-life of 17 to 30 years in humans. In fact, it has been claimed that approximately one-third of the cadmium accumulated in the body of an adult was absorbed during the first few years of life (*3*). A possible explanation of this claim could be the increased amount of milk ingested during infancy. Research has

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Abbreviations used: δ-ALA, delta-aminolevulinic acid; δ-ALAD, delta-aminolevulinic acid dehydratase; As(III), arsenite (trivalent arsenic); As(V), arsenate (pentavalent arsenic); ATP, adenosine triphosphate; CH_3HgX, organic mercury; CNS, central nervous system; DMA, dimethylarsenic acid, GSH, glutathione; Hg^0, elemental mercury; Hg^{2+}, inorganic mercuric ion; MMA, monomethylarsonic acid; MT, metallothionein; PKC, protein kinase C.

shown that whole-body retention of orally administered ^{109}Cd in rats was about 15 times greater in milk-fed animals than in those receiving normal diets from 3 to 52 weeks of age (*4*). Because retention of nonorally administered cadmium was not affected by this diet, it is apparent that a diet consisting entirely of milk influences cadmium metabolism only at the intestinal level. The high absorption in the young may result from pinocytotic absorption of proteins and other macromolecules (*5*). The effect of the milk diet could be related to the binding of cadmium to these proteins. Therefore, the increased intestinal absorption of cadmium in the presence of a milk diet is probably attributable to the specific transport ligands present in the milk.

As previously mentioned, cadmium is a nonessential and toxic metal found throughout the environment. Cadmium interacts with the metabolism of four metals essential to nutrition: zinc, iron, calcium, and copper (*1,6–10*). Table 1 shows major cadmium interactions with these micronutrients and other dietary components. Another important nutritional aspect of cadmium is its interaction with the sulfhydryl-rich protein MT (*11,12*). These and other factors are important in determining the susceptibility of an individual to cadmium toxicity.

Table 1. Major cadmium interactions with micronutrients and other dietary components.

Metal		Toxicity
Cd		Anemia; osteoporosis; proximal tubular disfunction leading to hypertension, coronary artery disease, and chronic pulmonary diseases
Metal–nutrient	**Interaction and mechanism**	**Effect of nutrient on metal toxicity**
Cd–zinc	Competes for GI absorption; Cd interferes with zinc metabolism	Reverses Cd toxicity (i.e., decreases growth, increases lesions and testicular necrosis)
Cd–iron	Cd decreases iron absorption and metabolism (Cd possibly binds with ferritin and transferrin)	Supplementation corrects anemia: increases hematocrit and increases hemoglobin levels
Cd–calcium	Cd decreases intestinal calcium transport; increases Cd deposits in bone tissue in a calcium-deficient state	Sufficiency protects against bone deformities, osteomalacia, and osteoporosis (Itai-Itai disease)
Cd–copper	Cd interferes with copper metabolism, possibly by decreasing copper absorption	Corrects Cd-induced decreased plasma ceruloplasmin concentrations
Cd–protein	Low-protein diet results in increased Cd uptake	Sufficiency prevents Cd-induced decreased growth, decreases MT synthesis, and increases bone deformities
Cd–selenium	Selenium shifts Cd binding to higher molecular weight proteins	MT can now bind essential nutrients

GI, gastrointestinal.

Cadmium–Zinc Interactions

Probably one of the most well recognized and well studied metal–metal interactions in the human body is that which occurs between zinc and cadmium. There are many similarities between the two metals. Both cadmium and zinc are members of the group IIB metals. Both metals have a similar tendency to form tetrahedral complexes. Therefore, it seems likely that the two metals would have similar interactions with the human body. Evidence of support for this theory comes from various sources. The sites of absorption for cadmium occur mainly in the duodenum and early jejunum, whereas zinc is absorbed in the jejunum and ileum (*13*). Cadmium has an inhibitory effect on the activity of zinc-containing enzymes such as carboxypeptidase (*14*) and α-mannosidase (*15*). Indeed, cadmium replaces zinc in MT (*1*). There are claims of activity reductions of other zinc-containing enzymes that could be pertinent to the toxicity associated with cadmium. Cadmium reduces renal leucine aminopeptidase activity *in vivo*, an activity that might be responsible for the development of proteinuria (*16*).

The toxicity of cadmium may result from disturbances in zinc metabolism, leading to the description of cadmium as an antimetabolite of zinc (*17*). If the diet contains inadequate amounts of zinc, toxicity from cadmium exposure can be induced at much lower cadmium intake levels than from a diet containing adequate zinc levels. This can be attributed to the observation that high levels of dietary cadmium lead to decreased absorption and tissue levels of zinc. Furthermore, some of the symptoms of chronic cadmium toxicity are similar to those of zinc deficiency (*18*). For example, growth failure (*19*), parakeratotic lesions (*20*), and impaired glucose tolerance (*21*) occur in both cases. Cadmium-induced testicular damage arises from competition between cadmium and zinc for binding sites on essential enzymes required for gametogenesis (*22*). In rat studies, when dietary zinc is low (5 ppm), pathologic lesions in the liver, lung, heart, and testes were found (*23*) even though the kidney has been identified as the target organ for cadmium accumulation (*24*). In fact, the renal proximal convoluted tubules of Sprague-Dawley rats fed a zinc-deficient diet containing 100 ppm cadmium develop degenerative changes such as cytoplasmic vacuolation, mitochondrial swelling, and coagulative necrosis (*25*).

Symptoms of cadmium toxicity can be eliminated entirely by using a zinc supplement. This finding further demonstrates the antagonism between zinc and cadmium. The pathologic lesions caused by cadmium found in the liver, lung, heart, and testes of zinc-deficient rats can be dispelled when a 40-ppm zinc supplement is administered. Cadmium toxicity has also been reversed in chicks given zinc supplements (*26*). Zinc supplements are important during the last two trimesters of pregnancy because a significant decrease in plasma zinc levels has been observed in nonoccupationally cadmium-exposed women in southern Catalonia, Spain (*27*). The testicular necrosis described previously can be prevented by injection with zinc prior to cadmium exposure. Also, the ratio of zinc to cadmium concentrations is important in determining whether an industrial worker is susceptible to hypertension and/or coronary artery disease (*28*). The most compelling reason for the protective effects of zinc against cadmium toxicity is that zinc induces the production of the metal-binding protein MT (*29*). This cadmium-binding protein will be discussed later.

Cadmium–Iron Interactions

One of the symptoms associated with cadmium intoxication is the development of anemia in the exposed individual, a result of the inhibitory effect of cadmium on iron metabolism and absorption. Cadmium decreases hematocrit and hemoglobin levels in exposed workers. Rats receiving a diet

with 100 mg cadmium/kg for several weeks have shown reduced liver and kidney concentrations of iron (*29*). This could be attributable to the interference of cadmium with iron absorption at the intestinal level. Cadmium binds to liver ferritin, which is also present in the intestinal mucosa and involved in the mucosal uptake and transfer of iron. It has been suggested that higher gastrointestinal absorption of cadmium is due to lower body iron stores as measured by the concentrations of serum ferritin (*30*). The protein transferrin, which donates iron to the heme moiety in hemoglobin synthesis, binds to a variety of metals in addition to iron. Ferritin or transferrin could be involved in the cadmium–iron interaction observed during cadmium intoxication.

In rats, iron supplementation corrects the anemia caused by cadmium exposure (*31*). This is not surprising because cadmium produces the same type of anemia observed when the animal is iron deficient. Iron supplementation also eliminates other cadmium toxic effects such as reduced growth rate and lowered hemoglobin and hematocrit levels. An important result of research aimed at studying this iron–cadmium interaction showed that ascorbic acid protects markedly against anemia and growth depression produced in young Japanese quail receiving 75 ppm cadmium in the diet (*32*). Ascorbic acid does not have a direct effect on cadmium, but the nutrient improves iron absorption in the gastrointestinal tract. It has also been postulated that in addition to this effect, ascorbic acid plus iron might inhibit the intestinal absorption of cadmium (*7*).

Cadmium–Calcium Interactions

The interaction between cadmium and calcium was hardly recognized until development of the chronic cadmium syndrome, Itai-Itai disease, in Japan. This disease was characterized in a population of Japanese women by the development of bone deformities, osteomalacia, and an increased risk of contracting osteoporosis (*33*). These unfortunate women have an increased risk of developing Itai-Itai disease because their normal diet, which consists mostly of rice and other grains, is deficient in calcium. In rats, cadmium has an inhibitory effect on intestinal calcium transport that is stimulated by vitamin D (*34*). The bone deformities have been attributed to cadmium deposits in bone tissue that interfere with calcification, decalcification, and bone remodeling (*35*). Another sign of cadmium toxicity with regard to calcium is the hypercalciuria seen in most women with Itai-Itai. This increased urinary excretion of calcium could be attributable to a direct interaction of cadmium with the calcium reabsorption process or to the toxic actions of cadmium against the renal tubules in general. As has been stressed for zinc and iron, an adequate supply of calcium protects against symptoms of cadmium toxicity. The microbial enzyme phytase improves the apparent absorption of calcium and magnesium in albino rats while lowering liver and kidney cadmium accumulation (*36*).

Cadmium–Copper Interactions

Dietary supplementation with copper can reduce the mortality rate and severity of anemia in experimental animals receiving large amounts of cadmium in their diet. Copper metabolism was seriously disturbed in pregnant ewes receiving cadmium in their diet. Both liver and plasma copper concentrations were markedly reduced, as evidenced by deterioration of the wool (*37*). The most obvious disturbance in copper metabolism caused by cadmium is the reduced plasma ceruloplasmin concentrations (*37*). Ceruloplasmin is the protein responsible for transporting copper throughout the circulatory system. This drop in copper and ceruloplasmin levels is indicative of copper deficiency and can be eliminated by increasing dietary copper intake. This work was important because the levels of cadmium fed to lambs simulated typical conditions found in contaminated pastures in the vicinity of industrial complexes. This study emphasizes the link between environmental exposure to heavy metals and nutritional problems. Another explanation for the cadmium–copper interaction is that the two metals compete for binding sites on MT (*38*). Copper displaces cadmium from MT because of its higher affinity for the protein (*39*). This is evident in the pork industry in which pigs fed an excess of copper retained cadmium in kidney, liver, and muscle (*40*).

Cadmium–Metallothionein Interactions

Incorporation of cadmium in the sulfhydryl (cysteine)-rich protein MT is one of the principal detoxification mechanisms against the metal. MT is specific not only for binding cadmium but also for binding copper, mercury, silver, and zinc. In fact, MT synthesis is induced by the presence of these metals as evidenced by increases in MT mRNA (*41*). The main physiologic role of MT is to act as a homeostatic control mechanism by controlling the metabolism of both copper and zinc. Therefore, binding of a nonessential metal such as cadmium to MT is a fortuitous result of the chemical similarity between cadmium and the essential trace metals. Cadmium has a higher affinity for MT and in fact displaces zinc from the cysteine binding sites but does not displace copper because this essential trace metal has higher MT affinity (*39*). The free essential trace metals could then stimulate the production of more MT or be excreted in the urine, which would explain the deficiencies in these two metals observed during cadmium exposure. Zinc and copper supplements are thought to act by inducing MT synthesis, which allows the body to be adequately supplied with enough MT to combat the cadmium insult.

Even though MT offers mostly protective effects against cadmium toxicity, there is evidence that it is indirectly involved in contributing to cadmium's main toxic effect: renal failure. In the urine of cadmium-dosed animals, a large amount of cadmium–MT complex was recovered, indicating that the kidney is not very efficient at MT reabsorption (*42*). This complex is somewhat retained by the kidney and the protein is rapidly degraded, leaving free cadmium to accumulate in the kidneys. Therefore, MT is the vehicle that transports cadmium to its toxic site of action, the kidney.

Other Cadmium–Nutrient Interactions

A low-protein diet also makes one more susceptible to cadmium toxicity. Feeding experimental animals a low-protein diet before cadmium administration results in increased cadmium uptake by the whole body, which leads to decreased growth and increased bone deformities (*43*). Another predisposing factor is that protein production decreases; in other words synthesis of MT, the primary cadmium detoxification protein, occurs at a much lower rate.

Nutritional studies have shown that selenium offers some protection against acute cadmium-induced toxicity. The protective effects of selenium probably come into play by the shifting of cadmium binding from MT to higher molecular-weight proteins (*44*). This allows MT to be unencumbered and therefore able to bind essential nutrients such as zinc and copper.

Studies also have been conducted on the effect of vitamins on cadmium toxicity. Although the exact mechanism is unknown,

vitamin C supplementation reduces elevated cadmium levels in the kidneys and livers of pigs fed a copper-rich diet (*40*). The addition of microbial phytase counteracted the decrease in growth and zinc status brought on by phytic acid and cadmium. Phytase also lowered liver and kidney cadmium concentrations (*45*). A significant attenuation of cadmium-induced tissue injury was observed in retinol-pretreated rats, possibly because of a 7-fold increase in MT production in the liver and less cadmium accumulation in the lung, kidney, and testis (*46*).

Nutrition and Its Effects on Lead Toxicity

Lead causes many adverse health affects, including toxicity of the nervous, hematopoietic, renal, endocrine, and skeletal systems, with the CNS as the primary target organ. Presently, impairment of cognitive and behavioral development in infants and young children is the toxic effect of greatest concern.

Toxicity, which is both age and lead dose dependent, occurs from low-level exposures from various environmental sources including air, food, and water. However, removal of leaded gasoline in the United States and other countries and elimination of lead-soldered cans in the canning of food products greatly reduced the extent of exposure from these sources. Lead-containing paint, used in older homes built before the 1970s or in urban, lower-income housing, is a major source of lead exposure for young children. These children may sustain many of the risk factors such as low socioeconomic status and calcium and iron insufficiencies known to intensify the manifestations of lead exposure. Lead toxicity, including its effects on the CNS, is known to occur with blood concentrations between 0.48 and 0.72 μmol/liter, and over 1 million children in the United States have blood concentrations in this range or higher (*47,48*). In the adult subpopulation, physiologic conditions associated with bone resorption, including pregnancy, lactation, and aging, can also potentiate the CNS effects of lead and enhance exposure.

Calcium supplements, wine, leaded crystal glass, and lead-containing glazed pottery are additional sources of lead exposure (*49,50*). Imported ceramics from Mexico, China, Korea, Italy, and Spain can release large amounts of lead into food and drink (*51*). Contamination from this pottery is now a leading public health problem in Mexico (*52*). Numerous studies have shown that the lead content of glazed ceramics used to prepare and store food is a major predictor of blood lead levels in Mexico, especially in children (*53,54*).

Lead–Calcium Interactions

Extensive clinical and experimental evidence supports the significance of lead–calcium interactions (*55*). These interactions occur at the cellular and molecular levels and are a result of the ability of lead to mimic or displace calcium during specific physiologic processes. Studies show that lead inhibits the release of neurotransmitters by blocking the entry of calcium into nerve terminals (*56,57*), by competing with calcium for uptake by calcium channels (*58,59*), and by inhibiting all subtypes of calcium channels (*60–62*). It is likely that lead blocks calcium efflux from cells by substituting for calcium in Ca^{2+}/Na^{+} adenosine triphosphate (ATP) pumps. This mechanism of interference could possibly explain how lead interacts with calcium in the intestine (*63,64*). Another critical interaction between lead and calcium occurs within cells, where lead interferes with calcium binding to receptors coupled with second messenger functions (*65–67*). This mechanism involves a competition between lead and calcium for calcium receptor proteins like calmodulin and protein kinase C (PKC). Lead acts by displacing the calcium bound to calmodulin and affecting the free concentration of calcium inside the nerve terminal, which leads to the stimulation of neurotransmitter release (*67–69*). Lead appears to have a better capacity to activate PKC, thus causing an increase in its activity. This can lead to increases in cell division and proliferation and increases in cellular responses to PKC such as cell–cell communications, cytoskeletal organization, and the release of neurotransmitters (*67,69–71*). Recent evidence also shows that lead alters inositol polyphosphate receptor binding in the rat brain, possibly resulting in altered intracellular calcium levels that may influence neuronal activity (*72*). Evidence for all these interactions suggests that lead-induced disruption of calcium homeostasis in the immature and developing brain may interfere with normal development (*73*).

Calcium Effects on Lead Absorption

Gastrointestinal lead absorption and retention constitutes the major pathway of lead intake (*74*) and depends on the micronutrient status of the gastrointestinal lumen. Adults absorb approximately 10% of ingested lead and small children absorb approximately 50% of ingested lead. This difference may be the result of a higher density of intestinal transport proteins during periods of high growth (*75*).

Absorbed lead enters the blood and reaches the bones and soft tissues of the body, including the liver, from which it is gradually excreted (*76*). Long-term studies indicate that lead is not excreted at the same rate as it is absorbed (*77,78*). Lead, which is excreted both in urine and feces, continuously accumulates in the body tissues with age.

Nutritional factors are thought to play an important role in lead poisoning. Enhanced susceptibility to lead intoxication in cases of dietary calcium deficiency has been attributed to increased intestinal absorption (*79*) and body lead retention (*80*). Calcium and lead compete for similar binding sites on intestinal mucosal proteins, which are important in the absorptive process (*81*). These shared binding sites on absorptive proteins would explain why sufficient dietary calcium decreases lead absorption. A study by Six and Goyer (*80*) has shown that rats fed a low-calcium diet containing varying amounts of lead had higher blood and tissue concentrations of lead than rats fed a normal-calcium diet. This study demonstrates that dietary calcium deficiency increases lead concentration in critical organs.

Other studies have also shown that absorption of lead by the gastrointestinal tract is inversely related to dietary calcium. A study of pregnant women in Mexico City (*82*) found that use of lead-glazed ceramics was associated with elevated blood lead levels and that consumption of tortillas (rich in calcium) lowered blood lead levels in women of lower socioeconomic status. This decrease was not significant, but consumption of milk products significantly decreased blood lead levels in women of higher socioeconomic status.

Studies on the effect of a dietary excess of calcium on lead toxicity (*83–85*) indicate that a small decrease in lead absorption and blood concentration can be achieved; however, this effect is not as dramatic as the effect of calcium insufficiency on lead uptake and retention. Therefore the achievement of adequate rather than excessive dietary calcium seems to be more useful in combating lead intoxication.

Lead and Bone Metabolism

More than 95% of the adult body burden of lead is in the bone (*86*). Therefore bone

metabolism plays as important a role as do absorption and excretion in the ultimate fate of lead in the human body (*87*).

Reviews on the influences of calcium, phosphorous, and vitamin D on the uptake of lead by bone are extensive (*75,86,88,89*). A study of postpartum women in Mexico City (*90*) determined that use of lead-glazed ceramic ware along with lower consumption of high calcium-containing foods contributed significantly to higher bone retention of lead. Studies in rats also show that a phosphorous-deficient diet increases lead retention and that calcium- and phosphorous-deficient diets have an additive effect on lead retention (*91*). Thus, evidence suggests that dietary calcium and phosphorous sufficiencies can have an additive inhibitory effect on the absorption and retention of lead (*92,93*).

Vitamin D not only increases intestinal calcium and phosphate absorption but also stimulates the coabsorption of other essential minerals like magnesium, iron, and zinc and the absorption of toxic metals such as lead (*88,94–96*). One effect of vitamin D that may be involved in increased intestinal absorption of lead is the induction of calcium-binding proteins by intestinal cells (*97*). Studies show that lead-binding properties of these calcium-binding proteins could indeed result in vitamin D enhancement of lead absorption and deposition in both the kidney and bone (*98*). Furthermore, when calcium levels are low, serum levels of the vitamin D hormone, 1,25-dihydroxy-vitamin D, are elevated to stimulate intestinal absorption of calcium and synthesis of calbindin-D, a calcium-binding protein (*99*). Thus, this provides another mechanism by which lead absorption could increase in times of calcium deficiency (*79,97*).

Following deposition in the bone, lead can be mobilized in response to both physiologic and pathologic conditions. Mobilization of long-term stores of lead from the maternal skeleton may be a major determinant in transfer of lead from mother to infant during pregnancy and lactation. Studies in rats indicate that lead stored in bone as a result of previous maternal exposure should be considered a major source of self intoxication and milk contamination in lactating mothers (*100*). A study in Sweden found a decrease in serum calcium levels and an increase in blood lead concentrations in pregnant women, possibly because of mobilization of lead from bone (*101*). After onset of menopause there can be a marked mobilization of calcium from bone and hormone replacement therapy may reduce the return of endogenous lead to the circulation (*102*).

Lead–Iron Interactions

Nutritional iron deficiency and iron deficiency during periods of rapid growth, such as infancy, in laboratory animals also enhances lead absorption and promotes lead toxicity. This is more evidence for concern that pregnant women and young children may be more susceptible to dietary lead (*103*). However, unlike calcium deficiency, iron deficiency in rodents does not appear to result in redistribution of lead to non-bone tissues (*104*); it only affects the gastrointestinal absorption of lead (*105*). A negative relationship between dietary iron intake and blood lead levels was also found in a study of preschool children (*106*). Iron deficiency is recognized worldwide as one of the most prevalent nutritional problems; impairment of cognitive function among iron-deficient children has also been recognized (*107,108*). However, the mechanism by which iron deficiency is associated with behavioral alterations is not clear.

The effects of lead and iron on the heme biosynthetic pathways have been extensively investigated and characterized. Lead inhibits two major enzymes of the heme biosynthetic pathway: delta-aminolevulinic acid dehydratase (δ-ALAD) and ferrochelatase. Furthermore, lead seems to raise delta-aminolevulinic acid (δ-ALA) synthase activity, which leads to an accumulation of δ-ALA (*109,110*). Lead interferes with mitochondrial energy metabolism, which is necessary to reduce ferric iron to ferrous iron before insertion of iron into the porphyrin ring. When iron deficiency is present, ferrochelatase is more sensitive to these effects of lead (*110*) and results in depression of hematopoiesis. Therefore, iron supplementation may prevent this toxic effect of lead on hematopoiesis.

Additional studies demonstrate the capacity of MT to attenuate the lead-induced inhibition of δ-ALAD (*111*). A recent study by Church et al. (*112*) suggests the existence of a MT-like protein in erythrocytes that binds lead and possibly protects against lead toxicity by rendering that lead unavailable for retention in target organs.

Other Lead–Nutrient Interactions

Several other dietary components affect the absorption of lead; these factors, along with calcium, iron, and vitamin D, may hold some promise in decreasing the severity of lead toxicity, especially in children. The major interactions between lead and these micronutrients as well as other dietary components are summarized in Miller et al. (*113*) presents an extensive review of interactions between lead and essential elements, but additional and more recent studies have been conducted. Regular meals as well as higher total food and fat intake have been associated with decreased gastrointestinal lead absorption (*114–117*). Zinc influences both tissue accumulation of lead and susceptibility to lead toxicity, particularly the inhibitory effects of lead on δ-ALAD (*103,118,119*). Studies show that as dietary zinc increases, lead absorption and its subsequent toxicity decrease, indicating that zinc exerts its effect on lead in the gastrointestinal tract. In addition, Flora et al. (*120*) determined that simultaneous administration of zinc and of the lead chelator, calcium disodium EDTA, results in potentiated chelation of lead. Recently the effect of selenium on lead-induced neurotoxicity was studied in rats. Selenium was shown to have a possible protective effect on lead inhibition of succinic dehydrogenase, acetylcholine esterase, and the sodium/potassium ATPase in the rat brain (*121*). Another study (*122*) demonstrated that selenium supplementation during chelation of lead in rats may be a useful adjunct in chelation treatment of lead intoxication caused by the activation of lead-inhibited δ-ALAD by selenium.

Experimental, epidemiologic, and clinical investigations have repeatedly shown that nutritional intervention can play an important role in the toxicity associated with lead, especially in more vulnerable populations. When lead exposures are overwhelming, nutritional factors probably do not prevent lead intoxication. However, low-level exposures to lead are of greatest concern in children, who experience more severe developmental effects than other subpopulations. Therefore, the importance of nutrition as a component of a preventative strategy is much greater for children and other susceptible subpopulations.

Nutrition and Its Effects on Mercury Toxicity

Mercury is one of the most common heavy metals present in our environment. It has been used for more than 3000 years in medicine and in industry. It has been used therapeutically as a cathartic, diuretic, anti-inflammatory, antiparasitic, vermifugan, and in dental amalgams as well as folk remedies. Although most of its medical uses

Table 2. Major lead interactions with micronutrients and other dietary components.

Metal		Toxicity
Pb		Impairment of cognitive functions (especially in children); CNS symptoms include irritability, confusion, lethargy, coma, and convulsions; hematopoiesis depression
Metal–nutrient	**Interaction and mechanism**	**Effect of nutrient on metal toxicity**
Pb–calcium	Competes for binding sites on intestinal mucosal proteins	Sufficiency decreases GI absorption of Pb and decreases concentration of Pb in critical organs
Pb–phosphorous	Mechanism unclear; phosphorous may interfere with Pb uptake by bone	Sufficiency decreases bone retention of Pb; in combination with calcium sufficiency, can have an additive inhibitory effect on Pb absorption and retention
Pb–vitamin D	Vitamin D increases intestinal absorption of calcium, phosphate, and Pb via induction of intestinal binding proteins	Enhances Pb absorption and deposition in kidney and bone, promoting Pb toxicity
Pb–iron	Competes for iron transport systems (i.e., ferritin) of the intestine	Supplementation may decrease Pb absorption and toxicity (i.e., hematopoiesis depression); does not affect redistribution of Pb to nonbone tissues
Pb–total fat intake Pb–total food intake Pb–frequency of intake	Involves complex mechanisms that are not yet clear	Greater intake and frequency of meals are associated with decreased Pb GI absorption, leading to decreased Pb toxicity
Pb–zinc	Competes for GI uptake, perhaps on the same MT-like transport protein	Supplementation decreases Pb GI absorption, decreases Pb tissue accumulation, and thus decreases Pb toxicity (i.e. inhibitory effects on δ-ALAD)
Pb–selenium	Selenium activates Pb-inhibited δ-ALAD	Useful as an adjunct in chelation treatment of Pb intoxication

have been discontinued, industrial uses of mercury such as in gold mining, paint, and battery manufacture are increasing (*123*).

Mercury exists in the environment as elemental mercury (Hg^0), organic mercury (i.e., CH_3HgX), and inorganic salts (i.e., Hg^{2+}). Hg^0 is used in thermometers, switches, and barometers. Hg^0 is poorly absorbed from the gastrointestinal tract but is almost completely absorbed through the respiratory tract, rapidly crossing the blood–brain barrier and causing neurotoxicity. Its vapor accounts for most occupational mercury exposures. At the cellular level the dissolved vapor is oxidized to Hg^{2+}, which causes nephrotoxicity. Hg^{2+} can be found in preservatives, dyes, and disinfectants. This form of mercury is hydrophilic and thus is the most nephrotoxic form, affecting mainly the straight segment of the proximal tubule. Hg^0 causes neurotoxic effects by increasing permeability of the plasma membrane to calcium (*124*). The mechanism of toxicity of inorganic mercury is by impairing mitochondrial function. Mercury possibly promotes mitochondrial membrane leakage and increases mitochondrial oxygen consumption with subsequent increased production of hydrogen peroxide (*124*). Methylmercury is the form most frequently involved in mercury food poisoning. Methylmercury, a byproduct of the chemical industry, is produced by methylation of inorganic mercury in aquatic sediments and soils (*125*). This is the form that affects fish in contaminated lakes or rivers. It is lipophilic and readily absorbed by inhalation, dermal contact, and ingestion (diet) and distributes within a few days to all tissues in the body. It crosses the blood–brain and placental barriers to reach its principal target tissue: the brain. The mechanism of toxicity of methylmercury is not yet known. Recent studies have suggested that cleavage of methylmercury gives rise to the generation of oxygen radicals, ultimately leading to lipid peroxidation and neuronal cell damage (*126*). The results of methylmercury neurotoxicity are damaged microtubule structures in injured cells; inhibition of astrocyte uptake of serotonin, aspartate, and glutamate; suppression of N-type and L-type calcium channels in PC12 cells; and suppression of the γ-amino-*n*-butyric acid receptor–channel complex activity in rat dorsal ganglion neurons (*126*). The biological half-life of methylmercury in human tissues is about 50 days, with elimination via conversion to inorganic mercury and its excretion in the urine (*125*).

Exposure to many heavy metals occurs through food primarily in two ways: ingesting metal-contaminated food (i.e., fish) and storing and cooking food in pottery painted with metal-containing paints. Exposure to mercury via foodstuffs has been studied in fish, duck eggs, and canned tuna as well as several different market baskets (the diet of people from a specific area or region) have been tested for mercury content around the world (*127–135*). Mercury levels have been determined mainly in fish and in fish-eating people of many countries including Canada and the United States. Shubat et al. (*128*) suggested that fishing and fish-preparation customs influence the potential for mercury exposure. These influential factors include the site of fishing (contaminated areas) and the fish tissues eaten. Cultural backgrounds (among immigrants, for example) influence the potential for mercury exposure first because of eating customs (may eat the whole fish with almost no waste) and second because of the language barrier, which may interfere with the understanding of rules about fishing and fish eating. Shubat et al. (*128*) found these problems with Laotian immigrants and refugees who settled in metropolitan areas of Minnesota. Mercury levels increase with the age and size of most species and tissues of marine organisms (*133*). Eating fish can also lead to indirect mercury exposure of children. Boischio and Henshel (*127*) reported that the placenta and mother's milk are important routes of mercury exposure in infants. Other foods have also been examined for mercury content and been found safe. A study in Taiwan by Jeng and Yang (*136*) found that duck eggs, which are commonly included in the diet, were safe from mercury contamination. Similarly, Yess (*137*) found that canned tuna had mercury below the U.S. Food and Drug Administration action level. Different market baskets have also been examined for total mercury (*136–142*). Most of the studies reported mercury levels below the provisional tolerable weekly intake or the acceptable daily intake proposed by the Food and Agricultural Organization of the United Nations (Rome, Italy) and the World Health Organization (5.0 μg/kg/day). However,

Chan et al. (*140*) found that the wildlife of the Canadian Arctic, which constitutes the traditional diet of indigenous people, is an important source of mercury exposure. Mercury levels in most of the animals exceed the average weekly intake of mercury.

Foodstuffs can also become contaminated during the preparation process. The use of ornamental ceramics (glazed pottery) to store and cook meals in many developing countries (i.e., Mexico) (*143*) is known to increase the risk of heavy metal exposure. Food can also become contaminated with heavy metals during its handling and storage with different kinds of papers and board materials. Castle et al. (*144*) studied different papers and board materials intended for food contact and chemicals with a potential to migrate to foods. In this study, mercury was not detected above the limits of determination of 0.4 mg/kg.

Mercury–Selenium Interactions

Selenium was discovered in 1817 by Jon Jakob Berzelius (*145*). It is a nonmetal with some metallic characteristics and it occurs in nature as selenides of lead, copper, mercury, and silver. Selenium is a required dietary element for health, but it is also a toxic material. Required selenium levels for good health are between 0.04 and 0.1 ppm (*145*). In general, levels of selenium of 5 to 10 mg/kg of food are considered toxic (*146*). The naturally occurring levels of selenium in foods are capable of modifying methylmercury toxicity (*147*). The first study reporting that selenium counteracted acute mercuric chloride toxicity was published in 1969 (*148*). At that time selenium was reported to be highly effective in treating chronic methylmercury toxicity (*149*). The concentration of selenium used (5 ppm) was below the recommended concentration of dietary selenium in contrast to the concentration of selenium needed to protect against inorganic mercury (around 40 ppm), which is above the nutritional range.

Selenium's mechanisms of protection against methylmercury and inorganic mercury may be different. Selenium protection against inorganic mercury may involve a variety of mechanisms such as the direct stoichiometric complexing of mercury to reduce its availability (*150*). The reduction of mercury availability has not been proven because mercury levels are not decreased by selenium. It may be possible that selenium interferes with the metabolism of inorganic mercury by reacting with the mercuric ion to form a compound that is less toxic than the mercuric ion. Experiments on mice indicate that the reaction between selenium and mercury ions depends on the presence of reactive selenium (*151*). Selenium influences the oxidation rate of Hg^0 to mercuric ions that seems to be species dependent (*146*). The protection of selenium against methylmercury is not clear. Methylmercury is degraded to mercuric ion. The rate of this process is also species dependent. Selenium may protect against methylmercury as described for inorganic mercury. There may also be another protective mechanism involving selenium. When methylmercury is degraded to inorganic mercury, the methyl moiety can also be further degraded by homolysis to methyl free radicals (*148*). These molecules may initiate a chain reaction peroxidation of various lipid constituents. These products result as part of the metal toxicity. Selenium-dependent glutathione (GSH) peroxidase protects the cells by catalyzing the reduction of hydrogen peroxide and other organic hydroperoxides to products of greater stability (*152*).

Mercury–Vitamin E Interactions

Vitamin E was first reported to protect against methylmercury toxicity in 1974 and it was shown that high levels of vitamin E decreased mortality in Japanese quail fed 30 ppm methylmercury (*153*). The mechanism of action of vitamin E is that of a scavenger of radicals that otherwise initiate methylmercury breakdown. Vitamin E also can react with methyl radicals that might be formed in the breakdown. Other antioxidants may then be expected to protect against not only mercury but also other metal-induced toxicities. However, the most effective action of vitamin E may be related to its location in the cell membranes (a result of its physicochemical properties) and to its ability to stabilize membranes by interacting with unsaturated fatty acid chains (*148*).

Other Mercury Interactions

Hydrogen peroxide contributes to the cytotoxicity of mercuric chloride *in vivo* and *in vitro*. The nonenzymatic scavenger for hydrogen peroxide, pyruvate, and the enzymatic scavenger, catalase, reduce mercury-induced cell injury (*124*). Methylmercury neurotoxicity is blocked by other oxygen radical scavengers such as GSH, catalase, and cysteine (*126*). Methionine also affects mercury toxicity (*154*). Methionine supplementation depresses methylmercury-induced weight loss and liver weight, depresses deposition of mercury, and prevents depression of blood GSH peroxidase in rats (*154*). Mercury also interacts with the metal-binding protein MT, a low-molecular-weight cytosolic protein. MTs and MT-like proteins protect the biologic system by binding metal ions. The *in vitro* affinity of metals for MT is the following: Zn < Cd < Cu < Hg (*39*). The presence of Zn and Cu as essential metals and Cd as a nonessential metal may affect mercury toxicity. MT-I and MT-II are present in most if not all cells of the body and are readily inducible both *in vivo* and *in vitro* (*155*). MT-III is present only in the brain, primarily in neurons, and seemingly is not inducible (*155*). A summary of interactions with micronutrients and other dietary components can be found in Table 3.

Responses to Mercury Toxicity

One of the toxic effects of mercury is oxidativelike toxicity. The exposure of tissues to oxidative stress often instigates an antioxidant response that defends against or limits the severity of the oxidative injury. The activity of the hydrogen-peroxide degrading enzyme, GSH peroxidase, is decreased after exposure to mercury, which may contribute to increased renal generation of hydrogen peroxide. Another enzyme, heme oxygenase, is markedly induced by mercury in the kidney at early time points and may indicate a protective response (*124*). As a possible antioxidant response, the members of the *bcl* genes, *bcl2* and *bclx*, are induced by mercury in the kidney (*124*). These genes protect against apoptotic cell death. The *bcl2* gene is efficacious against oxidant-induced cell damage and prevents cell death induced by GSH depletion and the resulting oxidative stress and lipid peroxidation (*124*). The *bclx* gene is induced 16 hr after mercury treatment in conjunction with *bcl2* and also protects against oxidant-induced cell death. The cellular site of expression of these two genes (*bcl2* mainly, *bclx* exclusively) is the cell mitochondria, which is significantly altered by mercury (*124*). The induction of these two genes may represent a cytoprotective response that may be particularly salutary to the mitochondrion.

Nutrition and Its Effects on Arsenic Toxicity

Arsenic is a naturally occurring element. Most exposure is through consumption of food and water. Although the mechanism of chronic arsenic toxicity is not known, studies of populations in Taiwan (*156*), Chile (*157,158*), and Mexico (*159*) living

Table 3. Major mercury interactions with micronutrients and other dietary components.

Metal		Toxicity
Hg		Nephrotoxicity (impairment of mitochondrial function of the straight segment of proximal tubule by inorganic Hg); neurotoxicity (Hg^0 increases permeability of plasma membrane to calcium)
Metal–nutrient	**Interaction and mechanism**	**Effect of nutrient on metal toxicity**
Hg–selenium		
Inorganic Hg–selenium	Complexing of Hg by selenium	Reduces Hg availability, leading to the formation of a less toxic mercuric compound
Organic Hg–selenium	Mechanism not clear; selenium may catalyze the reduction of H_2O_2 and organic hydroperoxides to products of greater stability	Protects the cell against Hg-induced cell injury (oxidative stress)
Hg–vitamin E	Vitamin E reacts with methyl radicals that might be formed in methylmercury breakdown	Inactivates radicals
	Vitamin E interacts with unsaturated fatty acid chains in cell membranes	Stabilizes cell membranes
	Vitamin E acts as a scavenger of radicals	Decreases the presence of radicals
Hg–amino acids		
Hg–cysteine	Cysteine acts as a scavenger for oxygen radicals that might be formed during methylmercury breakdown	Reduces Hg-induced cell injury
Hg–methionine	Unclear	Prevents depression of blood GSH peroxidase (rats); prevents deposition of Hg

in areas of endemically high arsenic (0.3 to 0.8 mg/liter drinking water) have shown at least one of the following toxic signs: hyperpigmentation, keratosis, skin cancer, or Blackfoot disease, a vascular disease that leads to gangrene in the extremities. Other populations exposed to similar arsenic levels in the United States did not exhibit these health effects (*160–162*). This has led to the suggestion that other factors may play roles in the expression of chronic arsenic toxicity, including differences in duration of exposure, form of arsenic, and nutritional status.

Cellular studies have shown that the extent and type of damage caused by arsenic depend on the form or species of arsenic. Although the pentavalent inorganic arsenate [As(V)] is most prevalent in the environment, it is considered less toxic than the trivalent inorganic arsenite [As(III)]. As(V), however, can be reduced to As(III) in the body. Although arsenate can substitute for phosphate, thereby interfering with ATP synthesis and energy production (*163*), arsenite interacts with thiols and affects many functional proteins (*164*). As reviewed by Thompson (*165*), inorganic arsenic in the body is methylated by methyltransferase using *S*-adenosylmethionine as the methyl donor. The methylated forms monomethylarsonic acid (MMA) and dimethylarsenic acid (DMA) are less toxic, have lower affinities for tissue constituents, and are excreted in the urine, thus making methylation a detoxification reaction. Ingestion of arsenic already in an organic form, such as arsenobetaine (a common contaminant in marine fish from the bioaccumulation of microbiologically unchanged into the urine (*166*). The order of toxicity of arsenic species in mammals appears to be As(III), As(V), MMA, DMA, then other organic arsenic.

Direct studies on the effects of nutrition on arsenic toxicity have been hindered by lack of an adequate animal model of chronic arsenic toxicity and carcinogenicity. Populations exhibiting arsenic toxicity have mainly been of low economic status and suffering from some form of malnutrition. Nutritional studies in Chile revealed food energy and total protein intakes below recommended daily allowances (*167*). Concerns about low-protein diets prompted a nutritional study by Engel and Receveur (*168*), which showed that the exposed population in Taiwan had protein and methionine intakes that met recommended levels. Questions have arisen about whether their cysteine and methionine levels (while adequate for normal populations) are below the methylation capacity needed to detoxify the extra arsenic burden (*169*). Mushak and Crocetti (*170*) have argued that theoretically these micronutrient levels still are adequate. The role of selenium deficiencies in arsenic-induced skin cancer has also been discussed (*171*). A comparative study by Valentine et al. (*172*) initially examined differences in selenium intakes between populations in rural northern Mexico and Edison, California, that were exposed to similar levels of arsenic in drinking water but exhibited different extents of toxicity. The study revealed that the only difference nutritionally from the recommended daily allowances was a greater lack of vitamin A in the Mexican study group. These human studies along with an understanding of how different forms of arsenic exert their toxicities, are metabolized and detoxified, and how else arsenic may affect the body, provide insight into how nutritional status may ameliorate or aggravate arsenic toxicity. Table 4 summarizes the major interactions between arsenic and micronutrients and other dietary components.

Effects of Diet on Mechanisms of Arsenic Toxicity

Arsenic in the form of arsenate is chemically similar to phosphate. It uncouples oxidative phosphorylation by substituting for phosphate in ATP synthesis (*163,173*). That phosphate and arsenate can share the same transport mechanism is indicated by the decrease in intestinal absorption of arsenic with phosphate infusion in the rat (*174*). Theoretically, dietary phosphate could outcompete arsenate uptake and decrease toxicity. Whereas phosphate loading has been used by some athletes to enhance performance (*175*), the use of this supplement to ameliorate arsenate toxicity has not been studied. Phosphorus is so abundant in natural foods that phosphorus deficiency almost never occurs naturally.

The chemical similarity between arsenic and selenium, an essential micronutrient, generally allows for antagonistic effects between these two metalloids (*176*); however, there seems to be synergistic toxicity between arsenic and methylated selenium species (*177*). Unlike with phosphate, there is no interaction between arsenic and selenium gastrointestinal absorption (*178*). Instead, selenium and arsenic each increase the biliary excretion of the other (*179*). Arsenic appears to abolish the anticarcinogenic effects of selenium (*180*) but can actually be therapeutic in alleviating

Table 4. Major arsenic interactions with micronutrients and other dietary components.

Metal		Toxicity
As		Hyperpigmentation; keratosis; skin cancer; vascular disease
Metal–nutrient	**Interaction and mechanism**	**Effect of nutrient on metal toxicity**
As–selenium	Antagonistic effects	Decreases teratogenic toxicity
As–cysteine As–methionine As–protein	Sulfur-amino acid content affects GSH levels; As binds thiol groups	GSH detoxifies As
As–methionine As–choline As–protein	Precursors of *S*-adenosyl methionine, which is used in methylation of As	Important for As detoxification
As–zinc	Mechanism unknown	Zinc pretreatment associated with increased As elimination
As–vitamin E As–vitamin A	Antioxidants scavenge oxygen radicals formed during As metabolism	Decreases damage to macromolecules and decreases chance of developing lung cancer
As–garlic extracts	As binds to sulfur moieties of garlic compounds	Leads to alternative As binding and decreases chromosomal aberrations

inorganic selenium toxicity (*181*). Selenium can also alleviate arsenic toxicity. Selenate partially prevents the uncoupling of oxidative phosphorylation by arsenate (*182*). Selenium also decreases the teratogenic toxicity of arsenate in hamsters when both salts are injected simultaneously (*183*). Therefore, adequate or even extra selenium in the diet may alleviate arsenic toxicity, whereas a selenium deficiency may aggravate arsenic toxicity. A selenium deficiency, however, does not explain the differences in arsenic toxicity between populations in Mexico and California, which were both exposed to similar arsenic levels in drinking water and had adequate selenium levels in their diets (*172*). Hair samples show decreases in selenium and iron levels through the progression of Blackfoot disease (*184*), perhaps implying a role for these nutrients after all.

Arsenite interacts with thiol-containing amino acids, peptides, and proteins (*185*). It exerts its cellular toxicity by binding to key sulfhydryl groups, which results in enzyme inhibition. GSH is a thiol peptide and antioxidant that plays an important role in many xenobiotic detoxification reactions including arsenic detoxification. Cellular toxicity is inversely related to intracellular GSH levels and is exacerbated by GSH depletion. GSH levels can be affected to a certain extent by nutritional status (*186*). Low sulfur amino acid content of the diet (i.e., cysteine or methionine) or more generally, low-protein diets, yield low GSH levels and more pronounced arsenite-induced cellular toxicity (*187*).

Effects of Diet on Arsenic Metabolism

A low-protein diet can aggravate toxicity in another way. Low dietary intake of methionine, choline, or proteins decreased arsenic excretion (especially urinary excretion of DMA) and increased the tissue retention of arsenic in rabbits (*188*). Diets deficient in methionine and choline decrease *S*-adenosylmethionine levels, therefore inhibiting methyltransferase reactions (*189*), i.e., arsenic detoxification reactions.

Arsenic can induce increases in MT levels (*190*), which implies that arsenic can be detoxified by this low-molecular-weight, cysteine-rich, metal-binding protein. Zinc-induced increases in MT, however, do not seem to be responsible for the protection against arsenic lethality in mice pretreated with zinc (*191*). Although the mechanism for this tolerance to arsenic toxicity is not known, zinc pretreatment was associated with increased elimination of arsenic.

Effects of Diet on Secondary Arsenic Toxic Effects

During arsenic metabolism oxygen radicals may be produced, possibly leading to damage of DNA, proteins, lipids, and other molecules. There is a positive correlation between lipid peroxidation and arsenic tissue concentrations in the livers, kidneys, and hearts of arsenite-treated rats (*192*). Arsenite induces the body's antioxidant activities in human fibroblasts (*193*). Arsenite induces heme oxygenase, leading to heme degradation, iron release, and decreases in the cytochrome P450 biotransformation enzymes important in both endogenous and xenobiotic metabolism (*194*). Superoxide dismutase activity was also increased by sodium arsenite treatment in human fibroblasts (*193*). Dietary antioxidants such as vitamins E and A may also alleviate arsenic toxicity. Addition of vitamin E could at least in part prevent the arsenite-induced killing of human fibroblasts (*195*). As mentioned previously a role for vitamin A deficiency in the expression of arsenic toxicity has been implied by the nutrition survey comparison between populations in Mexico and California (*172*). Dietary intake of fruits and vegetables, particularly yellow and light green vegetables (foods high in vitamin A precursors), was inversely associated with the odds ratio of lung cancer in tin miners exposed to arsenic and other risk factors (*196*).

Because of arsenic's affinity for protein sulfhydryls, many side effects can occur from enzyme inhibition. Chronic arsenite toxicity results in mitochondrial changes that block lipoic acid-dependent dehydrogenase, which in turn inhibits glycolysis and results in a demand for glucose and subsequently in hypoglycemia (*197*). Arsenicals also inhibit pyruvate dehydrogenase in gluconeogenesis (*198*). Carbohydrate depletion caused by gluconeogenesis depletion may therefore aggravate arsenic poisoning. Studies show starved rats were more sensitive to As(III) than rats with free access to food (*198*), although starvation would also affect other potentially important dietary factors. Inhibition of citric acid cycle enzymes and associated reactions in the β cells of mice appears to induce features of diabetes (*199*). It has been suggested that arsenic exposure may play a role in the development of diabetes mellitus because there is an association of the disease with arsenic in drinking water in Taiwan (*200*) and with arsenic from occupational exposure in copper smelter employees in Sweden (*201*).

Dietary supplements may also affect arsenic toxicity and carcinogenicity. Arsenite-induced bone marrow chromosomal aberrations were decreased in mice fed crude garlic extracts (*202*). This may be because of arsenite's affinity for the sulfur moieties in many of the chemical compounds found in garlic extract.

The effects of arsenic toxicity by other heavy metals or contaminants found in the diet are outside the scope of this discussion, but it is evident that nutritional status may play an important role in the expression of arsenic toxicity. The most important factor,

at least theoretically, is adequate protein intake for the detoxifying methylation reactions. Comparison studies have shown that antioxidants such as vitamin A may also be important in alleviating toxicity. Because studies of these highly exposed populations from developing countries are the basis for setting regulatory levels in other countries, the role of nutritional status on the effects of arsenic cannot be overlooked. More research is needed to determine which dietary factors may alleviate or exacerbate arsenic toxicity. Whether remediation of dietary deficiencies will be enough to handle the arsenic burden or whether nutrient levels above the recommended daily allowances will be necessary remains to be determined.

Conclusions

There have not been many studies designed specifically to address the effect of micronutrient status on toxicity from exposure to nonessential metals. Based on data from mechanistic studies, the ability of micronutrients to modulate the toxicity of metals is indisputable. Micronutrients interact with toxic metals at several points in the body: absorption and excretion of toxic metals; transport of metals in the body; binding to target proteins; metabolism and sequestration of toxic metals; and finally, in secondary mechanisms of toxicity (such as oxidative stress). Therefore, people eating a diet deficient in micronutrients will be predisposed to toxicity from nonessential metals.

The fact that dietary sufficiency can have a significant impact on toxicity of nonessential metals may greatly affect risk assessment for these metals. Epidemiologic studies used to set acceptable exposure levels for nonessential metals in the United States have been performed in other countries. The diets of individuals in these countries are far different from diets in the United States. Depending on the micronutrient content of the diet, toxicity may be significantly different in other countries than in the United States. An example is the development of Itai-Itai disease in calcium-deficient Japanese individuals exposed to cadmium. Studies that determine the impact of diet on toxicity will make risk assessment more accurate.

The possibilities provided by the interaction of diet with toxic metals are clear. We can no longer afford to ignore the effect of micronutrients on the health of humans and animals exposed to toxic metals. The typical remedy for toxic metal exposure has been to remove the exposure source. However, situations such as the arsenicism in India today will arise—situations in which millions of people are affected and it is impossible to remove everyone from exposure. In these cases dietary manipulation may provide the best defense and must be understood to be of use.

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